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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,365	07/07/2003	Christopher J. M. Meade	01-1364	7867

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,365	MEADE ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-11,13,19-38,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-11,13,19-38,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 26, 2008 has been entered.

This office action is a response to applicant's communication submitted November 26, 2008 wherein a translated foreign priority document is submitted. This application claims benefit of provisional application 60/407895, filed September 3, 2002, and claims priority to foreign application DE10230769.5, filed July 9, 2002.

Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 are pending in this application.

Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 as amended are examined on the merits herein.

Applicant's submission of a certified English translation of the foreign priority document DE10230769.5, is acknowledged. The translation is seen to provide written description under 35 USC 112, first paragraph for the claimed subject matter of all of instant claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44. Therefore the claims are given a priority date of July 9, 2002.

Applicant's arguments and foreign priority document, submitted November 26, 2002, with respect to the rejection of instant claims 1, 2, 4, 5, 7-11, 13, 19-38, 43, and 44 under 35 USC 103(a) for being obvious over Knowles et al. in view of Meissner et al., in view of Hill et al., have been fully considered and found to be persuasive to remove the rejection, as the perfected foreign priority is seen to provide a foreign priority date before the prior art date of Knowles et al. under 35 USC 102(e). Therefore the rejection is withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 7-11, 13, 19-25, 28-34, 36-38, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yeadon et al. (US pre-grant publication 2004/1047544, cited in PTO-892) in view of Meissner et al., (US patent 6706726, of record in previous action) in view of Hoffman et al. (US patent 6417190, cited in PTO-892, first published as WO00/03542, also included with PTO-892)

Yeadon et al. discloses an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent. (p. 1 paragraph 0011) The PDE4 inhibitors include tricyclic nitrogen heterocycles that are similar in structure to the claimed PDE4 inhibitors, (p. 2

paragraph 0020) and the anticholinergics include compounds having a similar structure to those recited in instant claim 1. (p. 3 paragraphs0049-0052) The compositions can include a pharmaceutically acceptable anion such as bromide. (p. 3 paragraph 0053) This pharmaceutical composition can be used to treat respiratory diseases including asthma, chronic or acute bronchoconstriction, chronic bronchitis, small airway obstruction, emphysema, and chronic obstructive pulmonary disease. (p. 4 paragraph 0068) The composition can be administered by inhalation as an aerosol spray either with or without a propellant, including various fluorochloroalkanes and hydrofluoroalkanes including 1,1,1,2-tetrafluoroethane, which is the propellant gas TG134a recited in instant claim 22. (p. 8 paragraph 0112) For use in an atomizer, the composition can be prepared as a solution containing the active compounds, propylene glycol, (a co-solvent according to instant claims 30-31) sterile water, ethanol, and sodium chloride. (p. 8 paragraph 0114) The overall dose of the active substances is preferably between 1 µg and 20 mg. (p. 9 paragraph 0115) The ratio of the two agents to one another will be determined by the potency of the individual compounds being used. (p. 9 paragraph 0116)

Yeadon et al. does not disclose a pharmaceutical combination comprising the specific anticlolinergics and PDE-4 inhibitors recited in instant claim 1. Yeadon et al. also does not disclose compositions having the exact doses and ratios of active substances recited in instant claims 8-11 or a propellant containing inhalable aerosol containing additional ingredients according to instant claim 23, or a propellant-free

inhalable solution having a pH of between 2 and 7 or 2 and 5 according to instant claims 26 and 27.

Meissner et al. discloses anticholinergic compounds of a general formula which includes **1** as an embodiment. (Example 1, column 10, lines 10-29) These agents are expected to be useful in the treatment of chronic obstructive pulmonary disease and asthma. (column 19, lines 63-65) Meissner et al. specifically discloses that these compounds may be administered by inhalation. (column 22, lines 26-29) Specific formulations described by Meissner et al. include an aerosol spray for use in an inhaler, (column 24, lines 40-55) an inhalable solution according to instant claims 25-29, 32, 33, 36, and 39 for use in an inhaler according to instant claim 42, (column 24, lines 58-67) and a powder comprising the active substance and lactose monohydrate. (column 25, lines 15-20)

Hoffmann et al. discloses tricyclic heterocycles that are selective PDE-4 inhibitors. (column 2 lines 8-12) These compounds have the same structure **2a** recited in the instant claims. (column 2 lines 2-46) These compounds can be used as their physiologically acceptable salts by the addition of inorganic or organic acids, including acids such as succinic, hydrobromic, acetic, fumaric, maleic, methanesulfonic, hydrochloric, and other acids recited in instant claim 28. (column 3 lines 22-30) Solutions of these compounds can contain preservatives such as p-hydroxybenzoates, and stabilizers such as alkali metal salts of EDTA. (column 5 lines 58-62) A therapeutically effective dose is between 10-300 mg. (column 6 lines 4-6)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition similar to those disclosed by Yeadon et al. comprising the anticholinergic drug of Meissner et al. in place of the anticholinergics disclosed by Knowles et al and to use this combination in the therapeutic method of claim 43. It would also have been obvious to one of ordinary skill in the art to prepare this composition as a propellant-containing aerosol containing additional ingredients as described in claim 23, or as a solvent-free inhalable aerosol as described in claims 25-39.

One of ordinary skill in the art would have been motivated to prepare the composition using the anticholinergic compound **1** of Meissner et al. in place of the anticholinergics of Knowles et al. because this compound is also an anticholinergic, is structurally similar to the compounds of Yeadon et al., and is useful for treating the same condition. (i.e. obstructive pulmonary disease) Similarly one of ordinary skill in the art would have been motivated to use the PDE-IV inhibitors of Hoffman et al. because they have the same function and closely similar structure to those used by Yeadon et al. One of ordinary skill in the art would have been motivated to prepare a propellant-containing aerosol containing additional ingredients as described by claim 23 because adding standard ingredients such as preservatives, stabilizers, and surfactants is standard practice in the art. One of ordinary skill in the art would have been motivated to prepare the composition as a propellant-free aerosol according to claims 25-29, 32, 33, and 36 because Meissner et al. discloses such a solution as a means for pulmonary delivery of the anticholinergic, and because Yeadon et al. also discloses such a solution

for use in an atomizer. One of ordinary skill in the art would have been motivated to use sodium EDTA in this solution because Meissner et al. discloses a solution comprising EDTA and sodium EDTA is a common form of EDTA. One of ordinary skill in the art would have been motivated to prepare the solution with only benzalkonium chloride or benzalkonium chloride and sodium EDTA because these solutions consist essentially of the same ingredients as the propellant-free solution disclosed by Meissner et al. and differ only in the absence of HCl, which is not essential to the biological function of the active ingredient.

One of ordinary skill in the art would have reasonably expected success in preparing the pharmaceutical composition with the compounds of Meissner et al. and Hoffman et al. because of the similarities between these compounds and those already known to be useful in this invention. One of ordinary skill in the art would have been motivated to make various minor modifications such as adding ingredients as described by claims 23, 30, 31, 34, and 35 or subtracting them as described in instant claims 18, 36, and 37 because these modifications are minor modifications which are well within the routine skill of one of ordinary skill in the art. Furthermore choosing specific amounts and ratios of the disclosed compounds, as described by Yeadon et al. above, is similarly within the ordinary level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious. Note that the rationale for combining the cited reference is substantially similar to the rationale which was previously affirmed on appeal in this application.

Claims 26, 27, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yeadon et al. in view of Meissner et al. in view of Hoffman et al. as applied to claims 1, 2, 4, 5, 7-11, 13, 19-25, 28-34, 36-38, 43, and 44 above, and further in view of Dreschel et al. (US pre-grant publication 2004/0019073, cited in PTO-892)

The disclosure of Yeadon et al. in view of Meissner et al. in view of Hoffman et al. Is discussed above. Yeadon et al. in view of Meissner et al. in view of Hoffman et al. does not disclose a composition having a pH range of between 2-5 or a composition comprising an antioxidant such as ascorbic acid, vitamin A, vitamin E, or tocopherol.

Dreschel et al. discloses propellant-free inhalable formulations of tiotropium in water. (p. 2 paragraphs 0014-0016) the formulation preferably has a pH of between 2.7 and 3.1 adjusted by the addition of pharmaceutically acceptable organic and inorganic acids. (p. 2 paragraphs 0023-0024) Preferred excipients include antioxidants such as ascorbic acid, vitamin A, vitamin E, and tocopherols. (p. 3 paragraph 0031) These solutions are intended for inhalation from an atomizer. (p. 4 paragraphs 0049-0055)

It would have been obvious for one of ordinary skill in the art at the time of the invention to prepare the compositions of Yeadon et al. in view of Meissner et al. in view of Hoffman et al. as propellant-free solutions according to Dreschel et al. containing the claimed antioxidants and having a pH of between 2.7 and 3.1. One of ordinary skill in the art would have been motivated to do so because Yeadon et al. in view of Meissner et al. in view of Hoffman et al. already discloses inhalable formulations including propellant-free solutions, which are similar to those described by Dreschel et al. One of ordinary skill in the art would reasonably have expected success because the

formulation of Dreschel et al. is already disclosed to be useful for delivery of pharmaceutical ingredients by inhalation, particularly anticholinergics.

Therefore the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
2/9/2009